An Update on the Role of Interim Restaging FDG-PET in Patients With Diffuse Large B-Cell Lymphoma and Hodgkin Lymphoma

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Abstract
A significant amount of literature is available on treatment monitoring and response assessment in lymphoma using FDG-PET, yet confusion exists concerning the potential and limitations of FDG-PET for determining the presence of residual disease during chemotherapy (interim FDG-PET). This article reviews the role of interim FDG-PET in 3 important scenarios: untreated diffuse large B-cell lymphoma, untreated Hodgkin lymphoma, and relapsed or refractory aggressive lymphoma in transplant-eligible patients, and provides recommendations on the use of this imaging modality in these settings. (JNCCN 2010;8:347–352)

Numerous chemotherapy strategies exist to improve progression-free survival (PFS) in patients with either Hodgkin lymphoma (HL) or diffuse large B-cell lymphoma (DLBCL), including dose–dense chemotherapy,1 infusional approaches,2 and the addition of newer agents to the backbone of standard therapy,3 as well as consolidated high-dose therapy (HDT) and autologous stem cell transplantation (ASCT).4 Randomized studies provide little evidence that these alternative and more-aggressive approaches are necessary in all patients, and therefore risk-adapted approaches have evolved.

Currently, pretreatment clinical or molecular prognostic models are used to stratify patients into favorable and unfavorable cohorts. Dose intensification of therapy is anticipated to improve outcomes in patients with unfavorable disease, whereas treatment attenuation will not negatively impact PFS in patients with favorable disease but rather may decrease long-term side effects associated with full-course therapy. Meta-analysis data in patients with DLBCL do not support the use of consolidative HDT and ASCT in this setting.5

Another research approach to risk-adapted therapy is to administer standard outpatient or inpatient regimens to all patients and then change or maintain therapy based on interim radiologic evaluation. Use of FDG-PET for assessing response is well established in DLBCL and HL, and has been incorporated into the consensus criteria of the International Harmonization Project in Lymphoma to determine remission status of these lymphomas.6,7

To use interim radiologic evaluation in the standard, nonprotocol management of aggressive lymphomas, both the negative and positive predictive value of the interim radiologic evaluation must be high. Data from multiple phase II studies using various treatments indicate that normalization of FDG-PET at interim restaging is associated with an excellent outcome.8–11 However, results are inconsistent in patients whose interim FDG-PET shows residual activity. Depending on the setting and histology, a positive interim FDG-PET scan has been associated with a favorable outcome in more than one third of patients, and therefore the positive predictive value of the interim evaluation is suboptimal.12

This manuscript reviews the most compelling data evaluating the use of interim restaging FDG-PET imaging
in patients with DLBCL and HL in both the de novo setting (i.e., after 2–4 cycles of primary therapy; earlier FDG-PET scan studies, such as those performed after 1 cycle of chemotherapy, are not clinically relevant) and after standard-dose salvage chemotherapy that is administered before transplantation.

**DLBCL (Untreated Disease)**

In 2009, primary therapy for DLBCL incorporated R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab) administered in a 2- or 3-week schedule. The number of treatment cycles and whether or not consolidation was administered varied between protocols and from country to country. Much of the reported data supporting the use of interim restaging FDG-PET does not include treatment with rituximab-based therapy and are currently not necessarily clinically useful; however, nearly all report a negative predictive value of greater than 80%. This article focuses only on programs that include rituximab.

Mikhaeel et al. reported on a mixed population of patients with aggressive lymphoma; 75 had either DLBCL or primary mediastinal large B-cell lymphoma and were treated with either R-CHOP or CHOP. The exact number of patients receiving rituximab was not reported. Interim FDG-PET was performed after 2 or 3 cycles of treatment. Nearly 90% of patients with negative interim restaging were progression-free. The remaining patients had frank FDG-PET positivity or minimal residual uptake; only 15 of the 52 patients in these subsets were progression-free.

Haioun et al. reported the results of 92 patients treated with either CHOP/R-CHOP or ACVB/P/R-ACVB (doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone/with rituximab) induction. The 2-year event-free survival of the 54 patients with negative FDG-PET interim restaging was 82%, compared with 43% in the 36 with a positive FDG-PET. For the 37 patients who received rituximab, the results were similar but not compelling ($P = .02$). Because nearly 50% of patients receiving rituximab-based therapy had done well in the FDG-PET–positive cohort, justifying a change to more aggressive treatment is difficult.

In a cohort of patients with aggressive non-Hodgkin’s lymphoma treated with combination chemotherapy regimens with rituximab, Han et al. reported on the impact of interim FDG-PET and outcome. Compared with previous reports in the pre-rituximab era, the addition of rituximab resulted in a further reduction in the positive predictive value; among 40 patients who had interim FDG-PET, 23 of 27 who had positive results and 10 of 13 who had negative results were progression-free.

Two R-CHOP series were recently reported. Cashen et al. reported on a cohort of 50 patients with DLBCL treated with R-CHOP for 6 cycles who underwent interim FDG-PET after cycle 2 or 3. Although follow-up was relatively short at only 15 months, the findings on the interim FDG-PET scan (positive vs. negative) showed no association with PFS; the negative predictive value was excellent at 85%, whereas the positive predictive value was poor at only 25%.

Furthermore, at the recent 2009 American Society of Hematology meetings in December 2009, Pregno et al. reported on 82 patients with DLBCL treated with R-CHOP for 6 to 8 cycles; all patients had an FDG-PET scan performed at diagnosis, during treatment (FDG-PET-2), and at the end of therapy (FDG-PET-3). All FDG-PET results were defined as positive or negative according to visual dichotomous consensus response criteria. At FDG-PET-2, 55 patients (67%) were negative and 27 (33%) were positive. At FDG-PET-3, 69 patients (84%) were negative and 13 (16%) positive. With a median follow-up of 18 months, FDG-PET-2 did not correlate with PFS ($P = .198$); however, at the end of study, FDG-PET-3 predicted PFS ($P = .015$).

At Memorial Sloan-Kettering Cancer Center, the authors completed a risk-adapted phase II study that included patients with stages II, III, or IV disease and 1 to 3 risk factors according to age-adjusted International Prognostic Index score. After induction therapy with 4 cycles of R-CHOP-14, all patients underwent FDG-PET. Patients who had negative FDG-PET results then received non–cross-resistant consolidative chemotherapy with 3 cycles of ICE (ifosfamide, carboplatin, etoposide).

This study is unique in that all patients who had a positive interim FDG-PET underwent biopsy of the FDG-positive site only if the FDG-PET was true positive as confirmed by histopathology showing DLBCL, and therapy was changed to 3 cycles of ICE and followed by an ASCT. However, if FDG-PET
was false-positive, with biopsy not showing lymphoma, patients received 3 cycles of ICE alone (i.e., the same treatment as the patients with a negative interim FDG-PET). In this study, the negative predictive value of interim PET was greater than 80%, but the positive predictive value was only 32%. No difference in outcome was seen between patients with true-negative and false-positive interim PET scans; both had a 3-year PFS of greater than 80%.

Based on available data, the authors currently recommend against changing therapy for patients with DLBCL treated with rituximab-based primary therapy without biopsy confirmation of a persistently elevated FDG uptake on the interim FDG-PET scan.

### Hodgkin Lymphoma (Untreated Disease)

Overall, the results of interim FDG-PET are more consistent in HL than in DLBCL. Minimal residual uptake, defined as low-grade FDG uptake (just above background) within an area of previously noted disease on interim FDG-PET scan, is likely a false-positive result in patients with HL, especially in early-stage disease in which 90% of patients are cured with standard therapy. This may cause more confusion in advanced-stage disease, in which the complete remission rate decreases significantly with an increase in the number of pretreatment clinical risk factors.

Treatment of HL with 6 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy induces long-term PFS rates of 75% in patients with advanced-stage disease. More aggressive therapy with BEACOPP regimens (bleomycin, etoposide, doxorubicin, vincristine, procarbazine, and prednisone) has shown an even greater efficacy, with cure rates approaching 85%, but is associated with increased risk for short- and long-term toxicity.

Gallamini et al. reported that interim FDG-PET was more effective than the International Prognostic Score (IPS) at predicting treatment outcome in patients with advanced-stage Hodgkin disease treated with ABVD. In their study of 260 patients with advanced-stage disease, FDG-PET was repeated after 2 cycles of ABVD treatment; treatment was continued unless disease progression was seen at this time point. At a median follow-up of 3 years, 43 patients experienced progression during therapy and 12 experienced relapse. After 2 cycles of treatment, 52 patients had positive FDG-PET results and 208 had negative. Of the 52 patients who had positive results, 44 (84.6%) ultimately showed treatment failure, either with progressive disease (n = 36) or relapse (n = 8); the remaining 8 are progression-free. Of the 208 patients who were FDG-PET negative after 2 cycles of treatment, 198 (96.6%) are still experiencing remission and only 11 had treatment failure.

The sensitivity of interim FDG-PET for predicting 2-year PFS was 77%, specificity was 96%, and overall accuracy was 92%. The only risk factors significant in multivariate analysis were stage IV disease (hazard ratio [HR], 2.2) and FDG-PET (HR, 21.8). Interestingly, the IPS score added no additional predictive value when FDG-PET was used. However, whether other groups of investigators will be able to reproduce these impressive results remains to be seen.

Based on these results, new trials are being initiated with risk-adapted therapy tailored to the patient’s pretreatment risk factors and interim FDG-PET response (Table 1).

### DLBCL and HL (Relapsed/Refractory Disease)

Randomized data support the use of HDT/ASCT for patients with chemosensitive relapsed or primary refractory DLBCL and HL. Despite the requirement of chemosensitivity to standard-dose salvage regimens such as ICE or DHAP, fewer than 50% of patients who undergo transplantation for relapsed and refractory aggressive lymphoma are cured with this regimen. This suggests that minimal residual disease is apparent, which then forms the basis for clinically apparent relapses. Accordingly, one would expect that patients who have residual viable disease on FDG-PET after salvage chemotherapy might have a worse outcome than those without demonstrable disease on FDG-PET.

This manuscript considers pre-ASCT FDG-PET scans as interim evaluation. Most patients undergo 3 cycles of salvage therapy, are restaged, and, if experiencing response, undergo definitive HDT. Historically, this interim evaluation was based on CT imaging. Although complete response on CT scans is consistent with an excellent response to therapy, patients with less than complete response on CT could perhaps be assessed better with FDG-PET. Unfortunately, the evidence for the predictive value of FDG PET in this setting remains somewhat limited.
had functional imaging and CT scans before high-dose chemotherapy. They saw no difference in outcome in the type of pretransplant functional imaging test used (Figure 1). Between October 1994 and February 2008, 198 patients received ICE salvage therapy on 1 of 4 consecutive protocols. The median follow-up for surviving patients was 7.4 years. The 5-year event-free and overall survival were 69% and 78%, respectively. A total of 76 patients (38%) had negative functional imaging and a normal CT scan response to ICE, 73 (37%) had a residual CT mass and a negative functional imaging response, and 49 (25%) had a positive response. The 5-year event-free and overall survival for the 3 groups were 86% and 93%, 71% and 79%, and 41% and 51%, respectively. A statistically significant improvement was seen in overall and event-free survival for the patients with negative pre-ASCT functional imaging versus those with a positive functional imaging ($P < .0001$).

Despite the documented clinical heterogeneity between studies, meta-analysis data confirmed the prognostic impact of pretransplant FDG-PET in patients with lymphoma. In retrospective data analysis for this distinct subset of patients, combining the data from gallium-67 and FDG-PET may perhaps be justified because both seem to provide prognostic information. On the other hand, there is no doubt that FDG-PET/CT is a much more advanced imaging technology, and larger data sets of transplant patients imaged in this manner are anticipated. For now, the authors believe that patients should not be excluded from a potentially curative treatment strategy based on pretransplant functional imaging findings alone. Although therapy should always aim to eliminate all demonstrable disease before ASCT, patients with abnormal functional imaging but documented improvement on CT still have a survival advantage with ASCT.

### Table 1 Trials Tailored to Pretreatment Risk Factors and Interim FDG-PET Response

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Induction</th>
<th>PET-Negative Consolidation</th>
<th>PET-Positive Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 50604</td>
<td>I/II Non-bulky</td>
<td>ABVD x 2</td>
<td>ABVD x 2</td>
<td>BEACOPP escalated x 2 and IFRT</td>
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<tr>
<td>CALGB 50801</td>
<td>I/II Bulky</td>
<td>ABVD x 2</td>
<td>ABVD x 4</td>
<td>BEACOPP-ESC x 4 and IFRT</td>
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<tr>
<td>SO816</td>
<td>III/IV</td>
<td>ABVD x 2</td>
<td>ABVD x 4</td>
<td>BEACOPP-ESC x 6</td>
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Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, vincristine, procarbazine, and prednisone; CALGB, Cancer and Leukemia Group B; IFRT, involved-field radiation therapy.
Summary

Interim evaluation of patients with aggressive lymphoma remains the subject of ongoing discussions and studies. Although initial data from the pre-rituximab era suggested that interim FDG-PET could separate patients into very favorable and unfavorable cohorts, more recent data are less conclusive. Data in patients with untreated ASHL suggest a marked survival disadvantage for patients who simply continue with ABVD-like therapy regimens in the setting of a positive interim FDG-PET. Whether escalation to more aggressive treatment regimens (e.g., BEACOPP) can improve their outcome will be addressed in a series of national and international clinical trials.

In the relapsed and refractory setting, HDT and ASCT is standard and curative therapy for HL and DLBCL. The goal of salvage therapy should be to administer pre-ASCT therapy to a maximal response (i.e., FDG-PET negativity) to improve survival.

References


